REMARKS

The Applicants have amended claim 1, canceled claim 10, and added claims 11-13. They address the rejections of the Office Action as follows.

The first rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-3 and 6 under 35 U.S.C. § 112, first paragraph, arguing that the specification, while being enabling for a method of treating Parkinson's disease and Alzheimer's disease, is not enabling for the treatment of all neurodegenerative disorders.

The Applicants have amended the claims such that they are now directed to a method of treating Parkinson's disease and Alzheimer's disease, thus mooting the rejection. The Applicants respectfully request that the Examiner withdraw it.

The second rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-9 under 35 U.S.C. § 112, first paragraph, arguing that the specification, while being enabling for a method of decreasing neuron loss following brimonidine treatment, does not reasonably enable a method of preventing death or degeneration of neurons. The Applicants respectfully disagree for the same reasons they have stated before: the specification teaches that, to prevent neuron death or degeneration, one administers brimonidine – and there is nothing in this method that requires undue experimentation to practice it.

The Examiner concedes that the inventors have showed that "brimonidine showed some improvement in the behavioral models and showed less neuron loss in MPTP treated animals," Office Action, at 7-8, but states that the inventors

> did not show total prevention of either Parkinson's disease or Alzheimer's disease . . . Further the specification does not teach a total prevention of neuron loss because there is still a measurable amount of neurons that have been depleted . . . A showing of prevention of any disease would require an unreasonable anticipation that a patient is

> going to have a particular disorder, i.e., Parkinson's or Alzheimer's disease.

Id. (emphasis in original). The Examiner applies an unreasonable standard. That the method of the invention "showed less neuron loss" is sufficient to achieve the claimed limitation of "prevent." There has never been a requirement that an invention be 100% successful, particularly in the medical arts. Were that the case, then no vaccine could ever be patentable, since at least some patients would still contract the disease they were immunized against; no analgesic could ever be patentable, since at least some patients would experience pain after taking it, and so on, until the vast repertoire of modern drugs would be rendered unpatentable by the Examiner's logic.

Preventing neuron death is one way that one can treat Parkinson's disease and Alzheimer's disease. The Examiner's position that one must show "total prevention" of neuron loss, so that no neuron loss ever occurs 100% of the time, depends on an unreasonable construction of the term "prevent." If one prevents some neuron loss, and no more than that, then one can successfully treat these conditions.

Consistent with this view is the labeling the FDA has adopted for drug products indicated for the "prevention of" diseases. Two examples are BONIVA®, which is "indicated for the treatment and prevention of osteoporosis," a disorder, like neurodegenerative disorders, that is progressive, and "FLUMIST,®" which is "intended for active immunization for the prevention of influenza" (the Applicants submit with this response the FDA-approved labels for each of these drugs). Yet BONIVA® does not prevent bone loss in all women, just a "majority" of them, and there is no evidence that BONIVA® prevents 100% of bone cells from dying. BONIVA® label, under the heading "Prevention of Postmenopausal Osteoporosis." Similarly, FLUMIST® does not prevent flu in all patients immunized with it, just most of them. FLUMIST® label, Tables 1 and 2. The Applicants attach to this response the labeling for these drugs.

If the FDA construed the term “prevent” in the same way as the Examiner, then one could never obtain an approval for a drug that prevents any disease. By preventing some neuron loss, one can treat Parkinson's disease and Alzheimer’s disease, and this use of the term “prevent” is consistent with the use in the medical community. The Applicants are entitled to a patent for such a discovery, and the Examiner has provided no evidence why any undue experimentation would be required to practice it.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the rejection under §112, first paragraph.

The rejection of claim 10 under 35 U.S.C. § 103(a)

The Examiner rejected claims 10 under 35 U.S.C. § 103(a), arguing that the claim is obvious in view of the Arnsten reference (*Science*, 230:1273-1276 (1985)) in combination with the Olejnik reference (U.S. Patent No. 6,627,210) and the Chan-Palay reference (J. Comp. Neurol., 287:373-392 (1989). The Applicants respectfully disagree.

The Arnsten reference is unremarkable. It does not stand for the proposition that clonidine can be used to treat neurodegenerative conditions.

First, Arnsten does not use an animal model of dementia or neurodegeneration. The experimental subjects are normal, aged animals:

> If loss of catecholamines contributes to age-related cognitive decline, then pharmacological treatments that facilitate their transmission may ameliorate the cognitive deficits. This hypothesis was investigated by examining the effects of catecholaminergic agonists on cognitive performance in five female rhesus monkeys ranging from 17 to over 30 years of age.

Arnsten, at 1274. There is no evidence that any of the animals have Alzheimer’s disease, Parkinson's disease, or any other neurodegenerative condition. The authors were investigating “age-related cognitive decline,” and their use of aged – but normal – animals is consistent with this purpose. Hence, we are left with nothing more than the observation that clonidine improves performance on a certain memory-related task in normal animals. What effect clonidine has on animals with neurodegenerative conditions is untested. Arnsten does not address this question. The premise of the Office Action that clonidine will have any effect in animals with neurodegenerative conditions is therefore nothing more than speculation.

Second, Arnsten provides no evidence that clonidine is effective in protecting neurons of the substantia nigra, ventral tegmental area, or locus coruleus, areas of the brain that experience significant neuronal loss in Alzheimer's disease and Parkinson's disease. Indeed, Arnsten shows precisely the opposite: that clonidine does not affect those areas, but affects the principal sulcul region, instead:

> The results of the depletion studies are consonant with clonidine acting at super-sensitive, postsynaptic α_2 receptors in the principal sulcal cortex. This idea was tested further by examining whether clonidine would remain effective in young adult animals in which the post-synaptic α_2-receptor population in the principal sulcal region had been removed surgically . . . in contrast with the aged [i.e., normal] monkeys, clonidine failed to improve the performance of these animals.

Arnsten, at 1275-1276. Neuronal loss in the substantia nigra, ventral tegmental area, or locus coruleus are associated with Alzheimer's disease and Parkinson's disease. See, e.g., Zarow et. al, Arch. Neurol. 60:337-341 (2003) ("For both AD and PD the greatest neuronal loss was found in the LC [locus coruleus]."); Attems et. al, Acta Neuropathol., 113(1):53-62 (2007) ("neuronal loss in SN [substantia nigra], partly related to tau lesions, is a major pathological substrate of EPS [extra-pyramidal symptoms] in AD."); Mann et. al, J. Neurol. Neurosurg. Psychiatry, 50(3):341-4 (1987) ("In 15 patients with Alzheimer's disease . . . there was severe atrophy, neurofibrillary degeneration and loss of pigmented dopaminergic nerve cells from ventral tegmental area whereas nerve cells in neighbouring substantia nigra were much less affected in all three respects.") (all of these references are attached hereto). Hence, Arnsten suggests that clonidine fails to target those areas of the brain that are most effected in Alzheimer’s disease and Parkinson's disease. For this reason, as well, there is no reason to believe that clonidine has any effect on treating neurodegenerative conditions.

The Examiner argues that

> Chan-Palay et al. teach that the locus ceruleus is an important source of norepinephrine and is implicated in Parkinson’s and Alzheimer’s disease and Arnsten et al. and Olejnik et al. teach that cell deterioration occurs in the locus ceruleus in Alzheimer’s disease and α_2-receptor agonists are a beneficial treatment. Because the combined references teach that both disease have similar pathologies, one would have a reasonable expectation of success that an α_2-receptor agonist would effectively treat both Alzheimer’s and Parkinson's disease.

The Examiner’s conclusion is unwarranted: to infer from the Chan-Palay or Oleknik references that alpha-2 agonists have any effect on neurodegeneration in Alzheimer’s disease and Parkinson's disease is speculation that is unsupported by those references.

Chan-Palay et al. found that there is degeneration in the locus ceruleus in certain patients with senile dementia of the Alzheimer’s type and in Parkinson's disease. They did not assess the action of alpha-2 agonists or any other agent for treating these diseases and say nothing about them.

The Olejnik reference discloses formulations for delivering alpha-2 agonists to the eye. It states that one can use “5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline” in the formulation, that is, one can use brimonidine, and that brimonidine is “an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.” But the Olejnik reference does not state what that neuroprotection is. The reference relates to formulations for delivery to the eye (for example: “in a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye," col. 3, lns. 30-35; see also col. 1, lns. 50-60), suggesting that the "neuroprotective activity" of Olejnik refers merely to protection of the nerves within the eye. The Olejnik reference does not suggest that one can treat neurodegenerative conditions; to do so with an ocular formulation would be most peculiar. And because the Olejnik reference does not identify the mechanism for the putative neuroprotection, it is further unclear as to what "neuroprotection" refers to. Moreover, the Olejnik reference discloses no data or other evidence to support the contention that brimonidine "has a neuroprotective activity." One of skill in the art, reviewing the Olejnik reference, would not conclude that brimonidine may be used to prevent or otherwise treat neurodegeneration of Alzheimer's disease or Parkinson's disease.

In sum, none of the references the examiner cites disclose or suggest that brimonidine may be used to treat the neurodegeration of Parkinson's disease or Alzheimer's disease. For this reason, the Applicants respectfully request that the Examiner withdraw the rejection under § 103.

The provisional double patenting rejection

The Examiner provisionally rejected claims 1-6 under the doctrine of obviousness-type double patenting, arguing that the claims are not patentably distinct from the claims of co-pending application no. 10/680,879. The Applicants respectfully disagree that the rejection is proper.

The co-pending application is directed to methods of treating Parkinson's disease and Alzheimer's disease by administering alpha-2B and alpha 2B/2C selective agonists. The present application, in contrast, administers brimonidine, an alpha-2 pan agonist. It is inappropriate to attribute to the alpha-2B and alpha-2B/2C agonists of the invention the properties of brimonidine, and vice versa.

That a compound is an alpha-2B or -2B/2C selective agonist does not mean that it will have the same activity as an alpha-2A agonist; the alpha-2A receptor and alpha-2B and -2C receptors are involved in different pathologies. According to Arnsten and Ramos, for example, "the α2A receptor subtype may be the most critical for cognitive enhancement." Arnsten and Ramos, Pharmacol. Ther. 113(3):523–536 (2007); see also Galeotti et al., Behav. Brain Res. 153(2):409-17 (2004). There are differences in other contexts, as well. For example, Stone, et al., J. Pharmacol Exp Ther. 323(3):899-906 (2007), claim that "Most alpha2 [adrenergic receptor] agonists require alpha(2A) [adrenergic receptor] activation to produce antinociception and opioid synergy." Höcker et al., Anesthesiology 109(1):95-100 (2008) found that meperidine, a compound for treating shivering, modulates the thermoregulatory response of alpha-2B and alpha-2C knock-out mice but has no effect on alpha-2A knock-out mice. Yoshitomi et al., Anesth. Analg. 107(1):96-101 (2008) showed that an alpha-2 pan antagonist but not an alpha-2B and 2C antagonist blocked the action of dexmedetomidine, suggesting that dexmedetomidine acts via alpha-2A receptors. Hence, that alpha-2B and alpha-2B/2C agonists have certain activity does not suggest that brimonidine will have the same activity.

For the foregoing reasons, the Applicants respectfully request that the Examiner withdraw the provisional double-patenting rejection.

The undersigned authorizes the Director to charge any fees required or necessary for the filing, processing or entering of this paper or any of the papers transmitted with it, and to refund any overpayment, to deposit account 01-0885.

Respectfully submitted,

/Joel B. German/

Joel B. German, Esq.
Attorney of Record
Registration No. 48,676

Please direct all correspondence and inquires to:

Joel B. German, Esq.
Allergan, Inc.
2525 Dupont Drive, T2-7H
Irvine, CA 92612
Tel: (714) 246- 4920
Fax: (714) 246-4249